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Lessons learnt from the variation across 6741 family/general practices in England in the use of treatments for hypogonadism

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What we knew

- Hypogonadism is increasingly being recognised as relevant to overall male health.
- However the rate of identification and treatment of hypogonadism even in developed health care economies remains low as as evidenced by Klinefelter Syndrome which affects approximately one in every 660 men but only 25% of the expected number of men are diagnosed with this condition, and of these only a minority are diagnosed before puberty.
- There are two main treatment options - injections or gels and these are used at various dose levels.

What we have learnt

- The largest volume (by prescribing amount) agents were injectable preparations at a total cost in 2018/19 of £8,172,519, with the gel preparations in second place at a total cost of £4,795,057. Transdermal patches, once the only alternative to testosterone injections or implants were little prescribed with the national annual cost being £222,022.
- There was a strong relation between PDE5-I prescribing and testosterone prescribing. Other factors independently linked with more testosterone prescribing were: HIGHER proportion of men with type 2 diabetes (T2DM) on target control and HIGHER overall practice rating on the National Patient Survey for ‘good experience’, while non-white ethnicity and socio-economic deprivation were associated with less testosterone prescribing. A number of comorbidity factors associated with less prescribing of testosterone (such as hypertension, T2DM and stroke/transient ischaemic attack (TIA)).

- The variation between general practices in prescribing of testosterone in a well organised developed health economy, is only related in a small degree (r^2=0.27) including 19 factors all with p values <0.05 to factors that we can define, as there is presently no universally accepted national guidance for the UK.

Abstract

Introduction

We have previously reported rates of diagnosis of male hypogonadism in United Kingdom (UK) general practices. We aimed to identify factors associated with testosterone prescribing in UK general practice.

Methods

We determined for 6741 general practices in England, the level of testosterone prescribing in men and the relation between volume of testosterone prescribing and 1) demographic characteristics of the practice 2) % patients with specific comorbidities 3) national GP patient survey results.

Results

The largest volume (by prescribing volume) agents were injectable preparations at a total cost in the 12-month period 2018/19 of £8,172,519 with gel preparations in second place: total cost £4,795,057. Transdermal patches, once the only alternative to testosterone injections/implants were little prescribed: total cost £222,022.

The analysis accounted for 0.27 of the variance in testosterone prescribing between general practices. Thus most of this variance was not accounted for by the analysis. There was a strong univariant relation ($r=0.95$, $p<0.001$) between PDE5-I prescribing and testosterone prescribing. Other multivariant factors independently linked with more testosterone prescribing were: HIGHER proportion of men with type 2 diabetes(T2DM) on target control (HbA1c ≤58 mmol/mol) and HIGHER overall practice rating on the National Patient Survey for good experience, while non-white ethnicity and socio-economic deprivation were associated with less testosterone prescribing. There were a number of comorbidity factors associated with less prescribing of testosterone (such as T2DM, hypertension and stroke/TIA).

Conclusion

Our analysis has indicated that variation between general practices in testosterone prescribing in a well developed health economy, is only related in small degree ($r^2=0.27$) to factors that we can define. This suggests that variation in amount of testosterone prescribed is largely related to general practitioner choice/other factors not studied and may be amenable to measures to increase knowledge/awareness of male hypogonadism, with implications for men's health.

Introduction

Hypogonadism (HG) in men has been associated with loss of sexual function, increased frailty and other co-morbidities including increased mortality (1). Hypogonadism itself is broadly referred to as testicular failure associated with androgen deficiency (2) although such a broad definition encompasses many men and has required sub-classification based on cause and age (3). The precise cut points on the basis of morning testosterone levels vary across guidance documents both within and between areas of the world (4,5,6,7). Moreover, reference ranges quoted by UK laboratories are not commonly derived from fasting samples only or from samples taken in the morning (<11:00 am) and are usually manufacturer derived (50%) or historical (18.8%) (8).

The rate of identification and treatment of hypogonadism even in developed health care economies remains low as evidenced by Klinefelter Syndrome which affects approximately one in every 660 men but only 25% of the expected number of men are diagnosed with this condition, and of these only a minority are diagnosed before puberty (9).

Testosterone is implicated in regulating metabolic functions, maintenance of muscle and bone, and inhibition of adipogenesis. In older individuals, reduced testosterone is associated with sarcopenia and sarcopenic obesity (4). Men with primary frailty, or primary obesity will necessarily exhibit lower testosterone levels as a normal physiological response. Several international guidelines recommend that all men with erectile dysfunction (ED), type 2 diabetes (T2DM), metabolic syndrome, and obesity (BMI >30 kg/m^2) should be routinely screened for HG (10,11,12) with ED and HG now recognised as independent risk factors for cardiovascular disease.(12,13) However the two Endocrine societies to have hitherto issued published guidance do not recommend routine screening in men with obesity, diabetes, or metabolic syndrome in the absence of other risk factors or clinical features (14,15)

The rate of identification and treatment of HG in the developed health care economies of the United Kingdom (UK) was recently reported (16). Some authors have suggested that

there is an “epidemic” of testosterone prescribing, prompting lively debate in the literature. There are two main treatment options - injections or gels and these are used at various dose levels (injections can also be used at different frequencies) (6,7). The treatment of HG often goes in tandem with treatment of ED with phosphodiesterase type 5-inhibitors (PDE5-Is) (17) which are shown to be of benefit for reducing cardiovascular risk in T2DM (17,18,19).

We previously reported rates of diagnosis of male hypogonadism in United Kingdom (UK) general practices (16). The reasons for the possible under treatment of hypogonadism in UK general practice are multiple. In order to gain a greater understanding of this, we here describe what are the determinants of testosterone prescribing at general practice level and the changes year on year in the balance of treatments used to treat male HG, while also analysing the changes year on year in testosterone prescribing overall.

Methods

We analysed data for general practices in England over the operational years 2011/12 to 2018/19, with a focus in detail on the final year 2018/19 (current year at the time of writing) as representative of prescribing practice.

We determined for each of 6741 general practices in England in 2018/19, the prescribing at a practice level of testosterone as described in Table 1.

Data Sources

Details about the location of each practice were obtained from the Office for National Statistics (ONS). General Practice Workforce Survey (20) provides details on the general practitioners in each practice and the following indicators were used. The Quality Outcomes Framework (QOF) (21) is the system that provides incentives to family doctor practices in the UK to manage a number of long term conditions. Each practice maintains registers of patients with specific conditions the % of total population was used for the following conditions. The National Diabetes Audit (22) provided information on the numbers and ages of people with diabetes.

Primary care prescribing data (24) was downloaded and assembled including the British National Formulary (BNF) code, quantity, items and costs of all prescriptions. This was linked to the Defined daily Dose (DDD), taken from the WHO ATC which is the assumed average maintenance dose per day for a drug used for its main indication in adults and is a widely used metric (24). Prescribing rates were adjusted according to DDD principles. The DDD is a statistical measure of drug consumption, defined by the World Health Organization Collaborating Centre for Drug Statistics Methodology.

Testosterone

- Number of different HG treatment applied (Number of different Testosterone medications used within the practice by method and dose)
- Testosterone % Injected (% of total Testosterone DDD)
- Testosterone Gel % dispensed by pumps (% of total Gel DDD)

PDE5-I

- Use of oral PDE5-I was calculated Annual Quantity prescribed as a ratio to males age >40 years
- Dose Level of PDE5-I was calculated from total DDD PDE5-I/Total Quantity of PDE5-I tablets

Details of these are given in Table 2.

Descriptive analysis

The actual number being treated within each practice was defined by the amount of testosterone being prescribed converted to the DDD (24), which is the assumed average maintenance dose per day for a drug used for its main indication in adults and is a widely used metric (24). WHO ATC values mg/DDD for testosterone parenterally, transdermally and orally were applied to amount contained within each BNF code times amount used.

The percentage expected hypogonadal patients for each practice were estimated from the expected prevalence by age group for Europeans by the European Male Ageing (EMAS) Study (3). The EMAS Study recruited 396/3369 (11.75%) of men from England.

To examine the link between use of PDE5-Is and testosterone, the use of testosterone was calculated by dividing the total actual amount in annualised DDD by the expected number of symptomatic HG patients calculated from linking the age prevalence given by Wu et al (3) with numbers of males by age group in each practice to give an overall % identified and treated. The % using PDE5-I was calculated by dividing the total quantity of tablets prescribed, by the number of male population age >40 and 52 (as NHS only allows prescription of 1 PDE5I tablet/week). The practices were then broken up into deciles of both PDE5-I and testosterone use. We did not have data concerning testosterone prescription for primary vs secondary hypgonadism.

Statistics

Multivariate backward stepwise linear regression analysis weighted by the population males aged >40 years was conducted to examine which factors independently linked with % of testosterone prescribing (dependent variable) at general practice level. The independent variables are described in Table 1. All of these are continuous except for number of testosterone preparations which is ordinal. A p value of <0.05 was taken as the cut point to consider as significant. We had in our full original assessment 25 factors that considered wide range of possible influences. We retained only those factors that kept a p-value <0.05. In the end 19 factors remained significant.

Practices finally included in the analysis had:

a) data for all the required fields
b) ≥500 total male population

The final number of practices included at each stage varied according to the specific analysis undertaken.

Data availability statement

All of the data that we used for the analysis is publically available. No patient level data was utilised for the analysis.

Results

Volume and cost of testosterone prescribing

The prescribing of testosterone for 6741 UK General Practices is shown in Table 2. The largest volume (by prescribing amount) agents were injectable preparations at a total cost in 2018/19 of £8,172,519, with the gel preparations in second place at a total cost of £4,795,057. Transdermal patches, once the only alternative to testosterone injections or implants were little prescribed with the national annual cost being £222,022. There were some testosterone tablets and implants used but in low volume accounting for £36,502 of costs annually (<0.5% of total).

The overall average cost/day of testosterone replacement in its entirety was £1.23.

Variation in prescribing

Data from 6,741 general practices were examined. There was great variation in practices in use of testosterone injections. While the mean was 63% of testosterone doses are given by injection, there were over 10% of practices who gave 100% by injection and over 10% who gave 0% as injection. The majority of the rest of the testosterone replacement was given as testosterone gel.

Change in testosterone prescribing year on year 2011 to 2018 (Figure 1)

The overall use of testosterone grew 45% from an average of 31,000 to 44,800 DDD/day over the years 2011 to 2018, with injectable preparations growing by 84% and transdermal preparations by 25%. The transdermal preparations have ~~has~~ moved from 93% in portion, sachets and tubes to now 76% by pump. Oral testosterone capsules have fallen from 5% to 0.9%.

How testosterone prescribing relates to possible need (Figures 2 and 3)

In Figure 2, we have shown for all the 6741 general practices included in the survey, the relation between the actual prescribing of testosterone replacement as defined daily dose

(DDD) and predicted prevalence of HG at the same general practice. This is plotted with each practice shown as a single point in Figure 3. The expected number of hypogonadal men in each practice is shown on the x-axis of Figure 3. The majority of practices prescribe no more than 20% of the predicted amount of testosterone that may be required on the basis of the number of men predicted to have a degree of HG. Only the practices with a lower expected prevalence of HG achieved even one third of the predicted need for testosterone

Relation of testosterone prescribing to PDE5-I prescribing at general practice level (Figure 4)

The prescribing of testosterone did relate closely to PDE5-I prescribing in univariate analysis (Figure 4) with r^2=0.89. There was a much greater variation across the general practices in testosterone prescribing compared with PDE5-I prescribing when compared with the median for the general practices (Figure 4) and as described next. For testosterone supplements, the lowest decile of prescribing categories was 30% of the median vs 250% of the median for the top decile = more than **8 fold differen**ce; vs PDE5-is, where the lowest decile was 60% of the median vs 150% of the median for the top decile = **2.5 times** difference between the lowest and highest decile.

Factors related to testosterone prescribing in multiple regression analysis (Figure 5)

The variance accounted for by the analysis, r^2 = 0.27, so much of the variance was not accounted for by the analysis of nationally available metrics as detailed as these are.

a) Prescribing behaviour of PDE5-is influenced the levels
b) General practice workforce (age, gender and country of qualification (COQ) of the general practitioner had little influence)
c) Poor local health reduced the level
d) Older age of men in the practice reduced the level
e) Some cultural factors (North/South, East/West, Urban/Rural, Ethnicity) had an influence on prescribing

f) Practices with a higher proportion of type 2 diabetes (T2DM) patients with good glycaemic control, prescribed more testosterone

There was a strong relation between PDE5-I prescribing and testosterone prescribing ($p<0.001$) for general practices. The analysis showed that the other factors independently linked with more testosterone prescribing were: HIGHER proportion of men with T2DM on target control ($p<0.001$) and HIGHER overall practice rating on the National Patient Survey (17) (for good experience ($p=0.008$) while non-white ethnicity (black and minority ethnicity (BAME)) ($p<0.001$) and income deprivation ($p<0.001$) were associated with less testosterone prescribing.

There were many comorbidity factors associated with greater prescribing of testosterone, specifically COPD and some comorbidity factors related to less prescribing of testosterone, specifically the proportion of individuals over 40 years old with T2DM in the practice ($p<0.001$) and more people on the hypertension and stroke/ transient ischaemic attack registers.

In relation to the characteristics of the general practice, practices with a higher proportion of younger general practioners tended to prescribe less testosterone as did general practices in the south vs the north of England, defined by their latitude.

Discussion

We found a strong relation ($r=0.21$, $p<0.001$) between PDE5-I prescribing and testosterone prescribing, which suggests that willingness to prescribe these agents to some degree may to some degree go hand in hand. Other factors independently linked with more testosterone prescribing were: HIGHER proportion of men with type 2 diabetes (T2DM) on target control (HbA1c ≤58 mmol/mol) and HIGHER overall practice rating on the National Patient Survey for good experience, while non-white ethnicity and socio-economic deprivation were associated with less testosterone prescribing. There were a

number of comorbidity factors associated with less prescribing of testosterone, such as T2DM and stroke/TIA.

The variation between general practices in prescribing of testosterone in a well organised developed health economy, is only related in a small degree, including 19 factors all with p values <0.05 to factors that we can define, implying that most prescribing is determined by doctor preference rather than any national guidance.

Restandol was prescribed but in low volume accounting for £113,074 of costs annually (<0.5% of total). Given that Restandol is ineffective as a testosterone replacement unless taken with a high fat meal, it is puzzling that it is still being prescribed in 267 practices. This may be because for a minority of men Restandol is the only form of testosterone replacement that they can tolerate.

Testosterone prescribing vs possible prevalence of hypogonadism – what can we do about this?

Figures 2 and 3 show the proportion of testosterone prescribed vs projected need. In relation to the novelty of our work, we accept that there is no register at a general practice level of men with hypogonadism. However we feel that the projections that we have made, are plausible. It should be pointed out that nay projections based on the EMAS findings (3,16) will always exceed the prevalence in NHS practice since there is a threshold (of unknown magnitude) which stops men with symptoms from seeking medical advice from their GP.

Although there is no justification for withholding testosterone treatment from older men with verified hypogonadism, there remain major concerns about the safety and benefit of prescribing testosterone to those older men whose low testosterone levels instead may likely reflect primary issues of frailty or comorbidity (25).

Discrepancies among the several available guidelines do not help to clarify the scenario (5). The debate on who should receive testosterone supplementation continues in the literature and elsewhere (26).

In fact only the practices with a lower expected prevalence of hypogonadism achieved even a third of the need for testosterone that we would predict from our modelling. Greater awareness of the importance of screening for hypogonadism and clear discussion support from the local hospital laboratories may help to address this as will awareness of the risks of leaving hypogonadism untreated (27,28). A recent paper pointed to a real risk of over diagnosis and unnecessary treatment with testosterone. It was pointed out that suboptimal sampling conditions can lead to misinterpretation of serum biochemistry with men not having verified as having hypogonadism being starged on therapy (26).

Nevertheless we feel that the differences that we report between general practices and potential determinants of the differences in testosterone prescribing at a general practice level are important findings. Unless there is a strong clinical context (e.g. a pubertal male with small testes) or raised LH level indicating organic testicular failure, at least 2 fasted early morning samples for serum testosterone should be taken (6,7,8), with addition of SHBG if necessary - in order to estimate circulating free testosterone (27) - before a diagnosis of hypogonadism is made.

Why is there such a difference between general practices in testosterone prescribing?

Our analysis has indicated that the variation between general practices in prescribing of testosterone in a well organised developed health economy, is only related in a small degree (r^2=0.27) to factors that we can define (Figure 5). This suggests that the variation in the amount of testosterone prescribed at a general practice level (adjusted for the number and proportion of older men) is largely related to the general practitioner choice / preference or other factors not available to our analysis, and therefore may be amenable

to measures to increase knowledge and awareness (5,16, 27,28) with a view to prescribing testosterone where appropriate.

Testosterone prescribing and awareness of sexual health

There was a strong univariate correlation between testosterone and PDE5-I prescribing at a GP practice level (Figure 4). This is not surprising as current expert guidelines recommend testosterone measurement for all men presenting with ED as well as screening all men with T2DM for low testosterone (3,4,5,6). It should be pointed out that in the case of men with T2DM, there are usually multifactorial causes of their ED, including vascular disease.

Unfortunately, there is no current guidance from NICE (the National Institute for Health and Care Excellence), the major organisation for change in UK practice. Over 7 years 2011 to 2018 there was increase overall in testosterone prescribing in England with an increase in the proportion of gel (increasingly gel delivered by pump) prescribed.

We found that the highest prescribing practices were prescribing 4 times as much PDE5-I and 2 times as much testosterone as the lowest prescribing practices for older men. This implies that the higher testosterone prescribing practices may have a greater awareness of male sexual health. Where appropriate testosterone supplementation and PDE5-I therapy, as we and others previously have shown, are associated with significantly reduced mortality and cardiovascular morbidity in men with T2DM (17,18,19,28). Further work is required in this area in relation to a dedicated randomised controlled trial (RCT) of PDE5-I therapy being conducted.

Prescribing patterns

The continued prescribing of oral preparations, such as Restandol in a few GP practices appears inappropriate as injections and gels show greater efficacy and fewer adverse events (7). The predominance of depot testosterone injection is indicative of the convenience of this mode of administration, although the market share of the gel preparations is growing year by year.

The unknowns

In multivariate analysis, good glycaemic control and good patient experience of their general practice were **positively** associated with testosterone prescribing while economic deprivation and high proportion non-white (BME) ethnicity were **negatively** associated. The relation between testosterone prescribing and comorbidities was complex as described in the results section and shown in Figure 5. A greater number of men over 40 with T2DM in a general practice, was associated strongly with less testosterone prescribing,. These findings merit further exploration beyond the scope of this paper.

In fact most of the variance in testosterone prescribing at 27% was not accounted for in our analysis – so 'doctor factors', are likely to be the major determinant.

This is much lower than in similar analyses where we examined through similar regressions links to use of other therapies such as antibiotics or anti depressants where r^2>0.5 were found (30.31).

All these factors and influences merit further investigation.

Strengths and Weaknesses

A significant strength of this paper is that we have used England national data for 2018/2019 covering all general practices. A weakness is that the data analysed is at general practice level, not individual patient level. Furthermore our study was not configured to look for factors beyond those reported in national level databases that may associate with the likelihood of a general practice to prescribe testosterone. We did not have access to data concerning rates of prostate cancer or polycythaemia. On the former point the consensus is that there is no evidence that testosterone treatment in hypogonadal man actually causes prostate cancer (32). Also we have not made any international comparisons (the topic of our next paper in this area).

We have made a number of assumptions, for example that our modelling of EMAS data of the likelihood of an older man being hypogonadal is valid in England in 2018/19, and that lower testosterone levels found in men with obesity and diabetes reflect an organic process of hypogonadism, rather than being a physiological epiphenomenon. Furthermore the volume of testosterone prescribed at any general practice can be affected by dosing frequency. Finally, we were not able here to look at specialist recommendations or hospital prescribing.

Conclusions

The level of awareness in the population and family doctors of the importance of screening for and treating HG, has significant consequences for both quality of life, longer term general health and mortality. If doctors are not prompting older males to consider these conditions and so are not detecting and treating the symptomatic patients then it is likely that the much higher proportion of less symptomatic patients may go undetected.

The variation in testosterone prescribed at a general practice level is largely related to the general practitioner choice and therefore may be amenable to measures to increase knowledge and awareness. More consistent prescribing of testosterone in the UK and in other health care systems, backed by robust national / international guidance and training that is independent of 'Pharma', so as to improve the quality of diagnosis, can only serve to improve the health prospects of men with hypogonadism at all stages of life.

Declaration of Interests

No author has any conflict of interest

Figure Legends:

Figure 1: Change in the balance of mode of testosterone supplementation prescribed between 2011 and 2018.

Figure 2: Variation in numbers pontetially needing treatment for HG and % being prescribing of testosterone across general practices in England 2018/19.

Figure 3: For all the 6741 general practices included in the survey (plotted by estimated number of men with hypogonadism), the relation between the actual prescribing of testosterone replacement as defined daily dose (DDD) and predicted prevalence of hypogonadism at the same general practice. The 95% control limits refer the Funnel Plot of the distribution of testosterone prescribing.

Figure 4: Relation between the prescribing of testosterone and phosphodiesterase type 5 inhibitors (PDE5-i) prescribing in univariate analysis ($r^2 = 0.95$).

Figure 5: General practice level regression for 6741 general practices in England, describing the factors linked to the prescribing of testosterone.
Definitions: PRESCR = prescription; PDE5-i = phosphodiesterase type 2–inhibitor; COPD = chronic obstructive pulmonary disease; QOF=quality outcomes framework; LOC = location; HbA1C = glycosylated haemoglobin; DM = diabetes mellitus; T2DM = type 2 diabetes mellitus; GPP + general practice survey; PRACT = practice; IDAOPI = Income Deprivation Affecting Older People score; HYP = hypertension; STIA = Stroke/Transient Attack; BME = black and minority ethnicity.

References

1. Rabijewski M, Papierska L, Kozakowski J, Zgliczyński W. The high prevalence of testosterone deficiency in population of Polish men over 65 years with erectile dysfunctions. Aging Male 2012; 15: 258-62

2. Rey RA, Grinspon RP, Gottlieb S, Pasqualini T, Knoblovits P, Aszpis S, Pacenza N, Stewart Usher J, Bergadá I, Campo SM. Male hypogonadism: an extended classification based on a developmental, endocrine physiology-based approach. Andrology 2013; 1: 3-16

3. Wu FC, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD, O'Neill TW, Bartfai G, Casanueva FF, Forti G, Giwercman A, Han TS, Kula K, Lean ME, Pendleton N, Punab M, Boonen S, Vanderschueren D, Labrie F, Huhtaniemi IT; EMAS Group. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010; 363: 123-354

4. Saad F, Röhrig G, von Haehling S, Traish A. Testosterone Deficiency and Testosterone Treatment in Older Men. Gerontology. 2017;63: 144-156

5. Tsametis CP, Isidori AM. Testosterone replacement therapy: For whom, when and how? Metabolism. 2018 Sep; 86: 69-78

6. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, Snyder PJ, Swerdloff RS, Wu FC, Yialamas MA. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2018; 103:1715–1744

7. Mulhall JP, Trost LW, Brannigan RE, Kurtz EG, Redmon JB, Chiles KA, Lightner DJ, Miner MM, Murad MH, Nelson CJ, Platz EA, Ramanathan LV, Lewis RW. Evaluation and Management of Testosterone Deficiency: AUA Guideline. J Urol 2018; 200: 423-32

8. Livingston M, Downie P, Hackett G, Marrington R, Heald A, Ramachandran S. An audit of the measurement and reporting of male testosterone levels in UK clinical biochemistry laboratories. Int J Clin Pract 2020; e13607

9. Bojesen A, Gravholt CH. Klinefelter syndrome in clinical practice. Nat Clin Pract Urol. 2007; 4: 192-204

10. American Diabetes Association. Statistics about Diabetes [Internet]. Arlington (VA): American Diabetes Association Available from: http://www.diabetes.org/diabetes-basics/statistics: accessed 1 January 2020

11. Hackett G, Kirby M, Wylie K, Heald AH, Ossei-Gerning N, Edwards D, Muneer A. The BSSM Guidelines on Erectile Dysfunction. J Sex Med. 2018; 15: 430-457

12. The American Association of Clinical Endocrinologists and American College of Endocrinology (2017) guidelines on the care of patients with Obesity. https://www.aace.com/publications/guidelines: accessed 17/02/19)

13. Hippisley-Cox J. Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ 2017; 357 doi: https://doi.org/10.1136/bmj.j2099 (Published 23 May 2017

14. https://www.endocrine.org/clinical-practice-guidelines: accessed 10 December 2020

15. https://www.mja.com.au/journal/2016/205/5/endocrine-society-australia-position-statement-male-hypogonadism-part-2: accessed 10 December 2020

16. Stedman M, Livingstone M, Albanese M, Hackett G, Heald AH. Hypogonadism is not being sufficiently recognised in 99% of general practices/family doctor surgeries. Int J Clin Pract. 2019 Nov 12:e13445. doi: 10.1111/ijcp.13445. [Epub ahead of print]

17. Hackett G, Heald AH, Sinclair A, Jones PW, Strange RC, Ramachandran S. Serum testosterone, testosterone replacement therapy and all-cause mortality in men with type 2 diabetes: retrospective consideration of the impact of PDE5 inhibitors and statins. Int J Clin Pract. 2016; 70: 244-53

18. Anderson SG, Hutchings DC, Woodward M, Rahimi K, Rutter MK, Kirby M, Hackett G, Trafford AW, Heald AH. Phosphodiesterase type-5 inhibitor use in type 2 diabetes is associated with a reduction in all-cause mortality. Heart 2016; 102: 1750-1756

19. Andersson DP, Trolle Lagerros Y, Grotta A, Bellocco R, Lehtihet MJ. Association between treatment for erectiledysfunction and death or cardiovas cular outcomes after myocardial infarction. Heart 2017;103:1264-1270 GP Practice

20. https://www.gp-patient.co.uk/: accessed 18 January 2020

21. https://qof.digital.nhs.uk/: accessed 19 January 2020

22. https://digital.nhs.uk/data-and-information/clinical-audits-and-registries/national-diabetes-audit: accessed 13 February 2020

23. GP Practice Prescribing Presentation-level Data. NHS Digital. https://digital.nhs.uk/catalogue. Accessed 13 February 2020

24. Defined Daily Dose (DDD); ATC/WHO. http://www.whocc. no/atc_ddd_index: Accessed 19 January 2020

25. Ross A, Bhasin S. Hypogonadism: Its Prevalence and Diagnosis. Urol Clin North Am. 2016 May; 43: 163-76

26. Al-Sharefi A, Wilkes S, Jayasena CN, Quinton R. How to manage low testosterone level in men: a guide for primary care. Br J Gen Prac 2020 Jun 25; 70: 364-365

27. Lunenfeld B, Mskhalaya G, Zitzmann M, Arver S, Kalinchenko S, Tishova Y, Morgentaler A. Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. Aging Male. 2015; 18: 5-15

28. Hackett G. Heald AH, Sinclair A, Jones PW, Strange RC, Ramachandran S. Serum Testosterone, Testosterone Replacement Therapy and All- cause Mortality in men with Type 2 Diabetes: Retrospective Consideration of the impact of PDE5 Inhibitors and Statins. Int J Clin Pract. 2016; 70: 244-53

29. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab. 1999; 84: 3666-72

30. Stedman M, Lunt M, Davies M, Fulton-McAlister E, Hussain A, van Staa T, Anderson SG. Heald AH. Controlling antibiotic usage-A national analysis of General Practitioner/Family Doctor practices links overall **antibiotic** levels to demography, geography, comorbidity factors with local discretionary prescribing choices. Int J Clin Pract. 2020 Apr 19:e13515. doi: 10.1111/ijcp.13515. Online ahead of print.PMID: 32306458

31. Heald AH, Stedman M, Davies M, Farman S, Upthegrove R, Taylor D, Gadsby R Influences on the use of antidepressants in primary care: All England general practice-level analysis of demographic, practice-level and prescriber factors. Hum

Psychopharmacol. 2020 Jun 3:e2741. doi: 10.1002/hup.2741. Online ahead of print.PMID: 32495350

32. Kaplan AL, Hu JC, Morgentaler A, Mulhall JP, Schulman CC, Montorsi F. Testosterone Therapy in Men With Prostate Cancer. Eur Urol. 2016 May; 69: 894-903

Factor		Median Value	Regression Coefficient /Model
SIZE-Male>40	Number of males on the practice list	1969	
Regression Constant	Constant from the regression calculation		-0.092
LOC-%Male>60	% of males on the list who are >60 in in age	44.5%	-0.27
LOC-North South Latitude%	Latitude value for the practice postcode	52.26	$4.2x10^{-3}$
LOC-East West Longitude	Longitude value for the practice postcode	-1.27	$-2.2x10^{-3}$
LOC-Urban/Rural Pop Density/sq km	Population density for local area of practice postcode	3,157	$-7.4x10^{-7}$
LOC-IDAOPI Income Deprivation Older People 2015	Income Deprivation Affecting Older People score for local area of the practice post code	17.0	$-4.9x10^{-4}$
LOC-GPP Survey % BME Ethnicity	Ethnicity given for responders to each practice patient survey	12.1%	-0.036
PRACT-GPP Survey % Overall Good Experience	% responded 'GOOD' when asked about overall experience in patient survey	84.5%	Not significant
PRACT-GPP Survey LTC % Confident	% who responded confident when asked about self management of their long term condition (LTC)	85.3%	0.021
PRACT-GP workforce FTE Gender % male	% general practitioners who are male in the workforce data for general practices	52.5%	Not significant

PRACT-GP workforceHC Age <40 Younger	**% general practitioners whose age<40 in the workforce data for general practices**	27.3%	-0.0099
PRACT-GP workforceHC Age >55 Older	**% general practitioners whose age >55 in the workforce data for general practices**	20.0%	Not significant
PRACT-GP workforceCOQ Non UK	**% general practitioners whose country of qualification (COQ) is not the UK in the workforce data for general practices**	16.7%	Not significant
HEALTH-QOF% Reg-CHD	**% of patients on practice coronary heart disease (CHD) register**	3.2%	Not significant
HEALTH-QOF% Reg-COPD	**% of patients practice chronic obstructive pulmonary disease (COPD) register**	1.9%	0.81
HEALTH-QOF% Reg-HF	**% of patients on practice heart failure (HF) register**	0.9%	Not significant
HEALTH-QOF% Reg-HYP	**% of patients who are on the practice hypertension (HYP) register**	14.6%	-0.17
HEALTH-QOF% Reg-OB	**% of patients on practice obesity = OB register**	8.0%	Not significant
HEALTH-QOF% Reg-PAD	**% of patients on the practice peripheral arterial disease (PAD) register**	0.6%	Not significant
HEALTH-QOF% Reg-STIA	**% of patients on practice stroke / transient ischaemic attack (STIA) register**	1.8%	-0.98
DM-DMT2 All Age%>65	**% of Patient with type 2 diabetes whose**	55.5%	-0.15

	Age>65		

Table 1: Factors included in the regression analysis.

Specific Delivery	Medicine	Name	Different Practices	Total Items	Total Quantity	Total DDD	Annualised DDD	Actual Costs
Capsule	Testosterone Undecanoate	Restandol Cap 40mg	770	6,088	425983	141,994	**389**	£113,074
ORAL			**770**	**6,088**	**425983**	**141,994**	**389**	**£113,074**
Injection	Testosterone Undecanoate	Nebido Inj 250mg/ml	6329	124,402	132018	7,334,333	**20,094**	£10,674,577
	Testosterone Enantate	Primoteston Inj Enantate 250mg/ml	1520	8,622	24794	344,361	**943**	£658,236
	Testosterone Esters	Sustanon Inj 250mg	3799	47,101	90802	1,261,139	**3,455**	£206,907
	Testosterone Propionate	Virormone Inj Propionate 50mg/ml	4	10	163	906	**2**	£7,147
INJECTED			**6624**	**180,135**	**247777**	**8,940,739**	**24,495**	**£11,546,867**
Sachet	Testosterone	Testim 50mg/5g Tube	2313	7,073	220035	220,035	**603**	£218,180
		Testogel Sachet 50mg/g	4897	34,823	1378283	1,378,283	**3,776**	£1,327,669

Pump	Testosterone	Testavan T/Derm Gel 20mg/g	45	79	8350	3,509	**10**	£2,353
		Testogel Pump 16.2mg/g	4658	75,884	8669321	3,085,823	**8,454**	£2,845,622
		Tostran Pump 2% (10mg/actuation)	5973	137,569	1.2E+07	2,315,875	**6,345**	£5,136,855
Tube	Testosterone Propionate	Testosterone Prop_Crm 1%	3	5	250	1,250	**3**	£1,275
GEL			**6745**	**255,433**	**2.2E+07**	**7,004,775**	**19,191**	**£9,531,953**
OVERALL TOTAL			**7142**	**441,656**	**2.3E+07**	**16,087,509**	**44,075**	**£21,191,894**

Table 2: Total Testosterone Prescribing 2018/19 for general practices in England. Annualised defined daily doses (DDD) and Totals for each mode of administration are shown in **bold.**

Figure 1

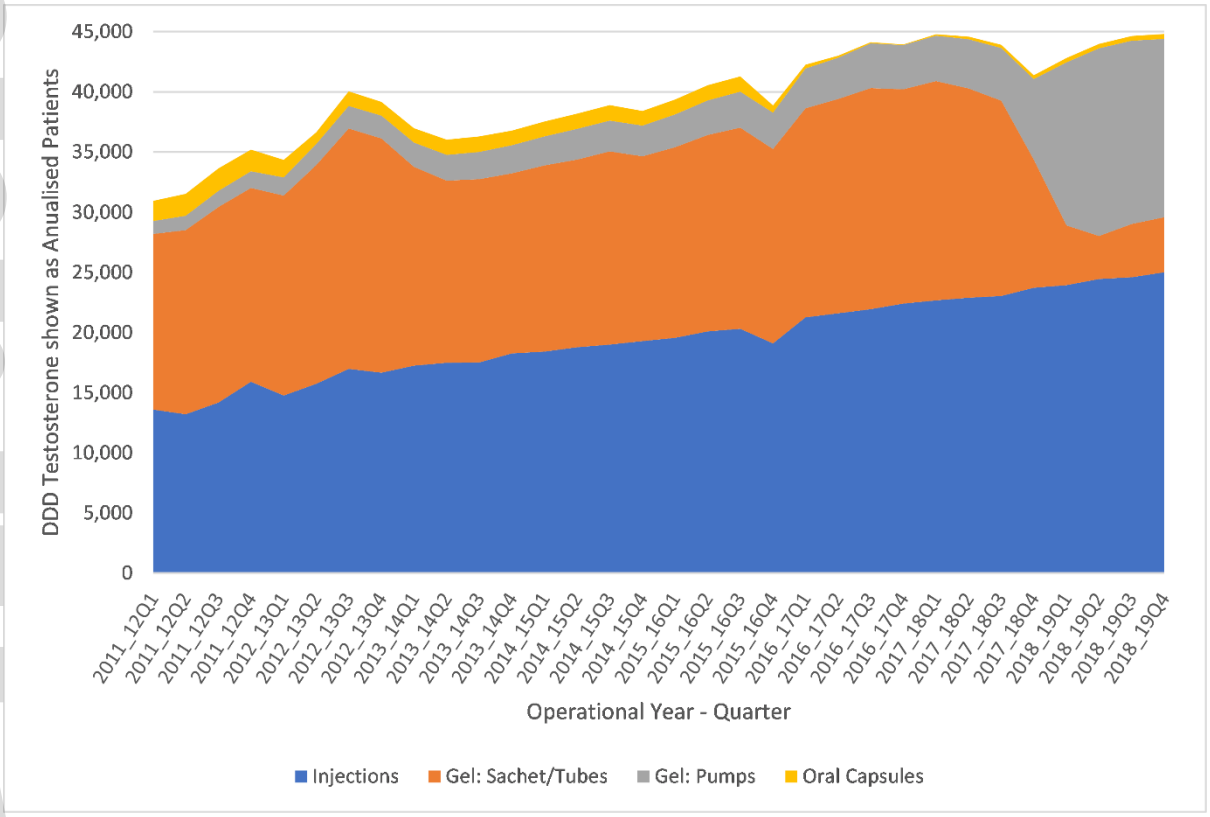

Figure 2

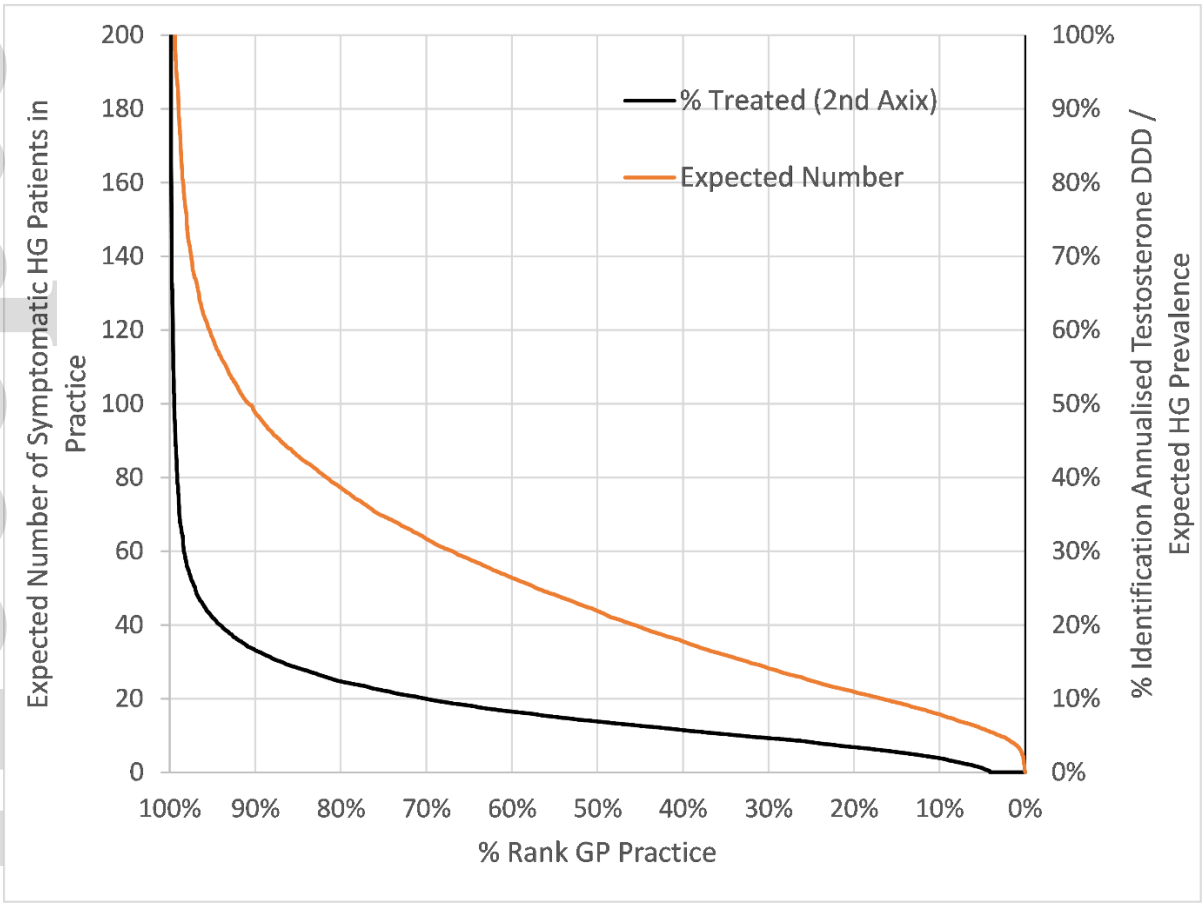

Figure 3

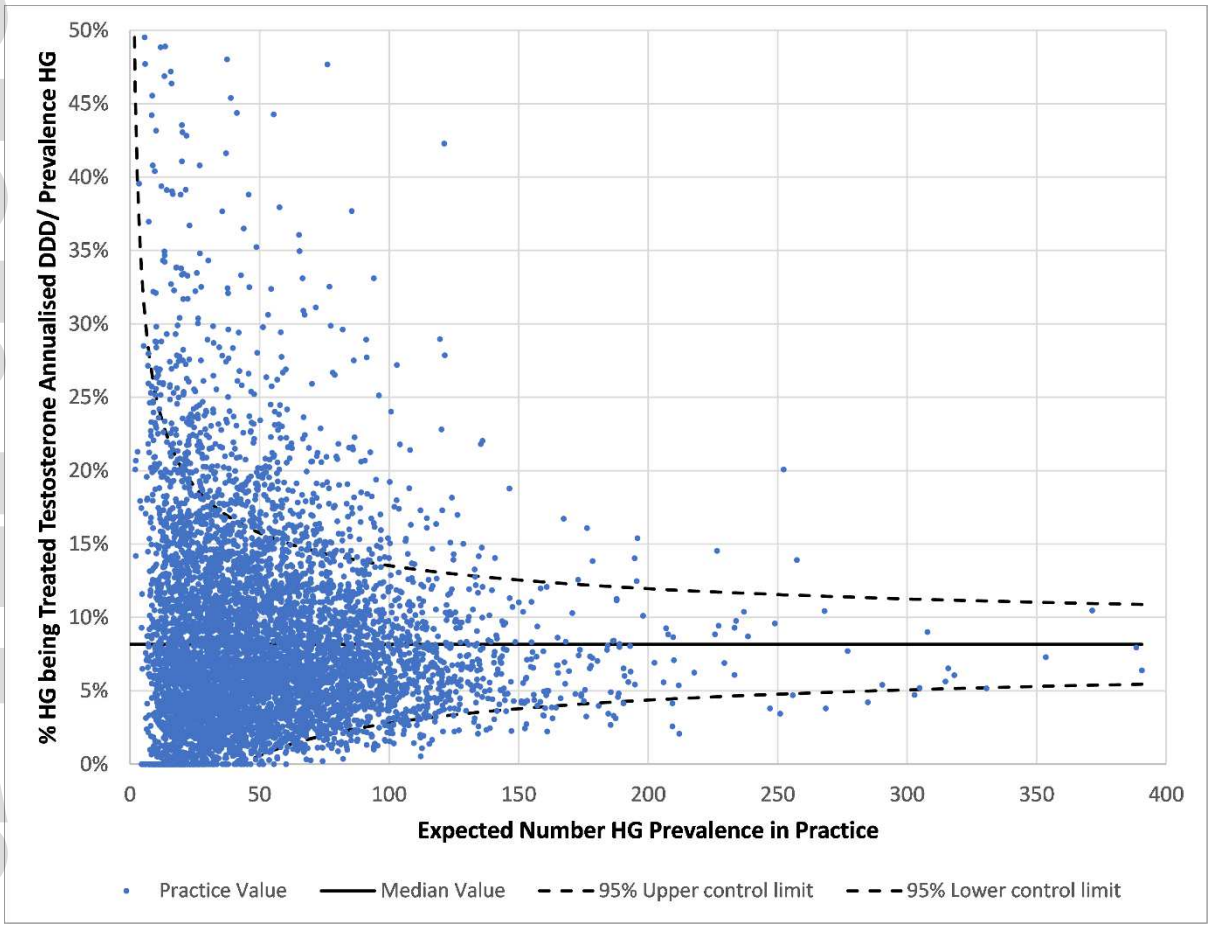

Figure 4

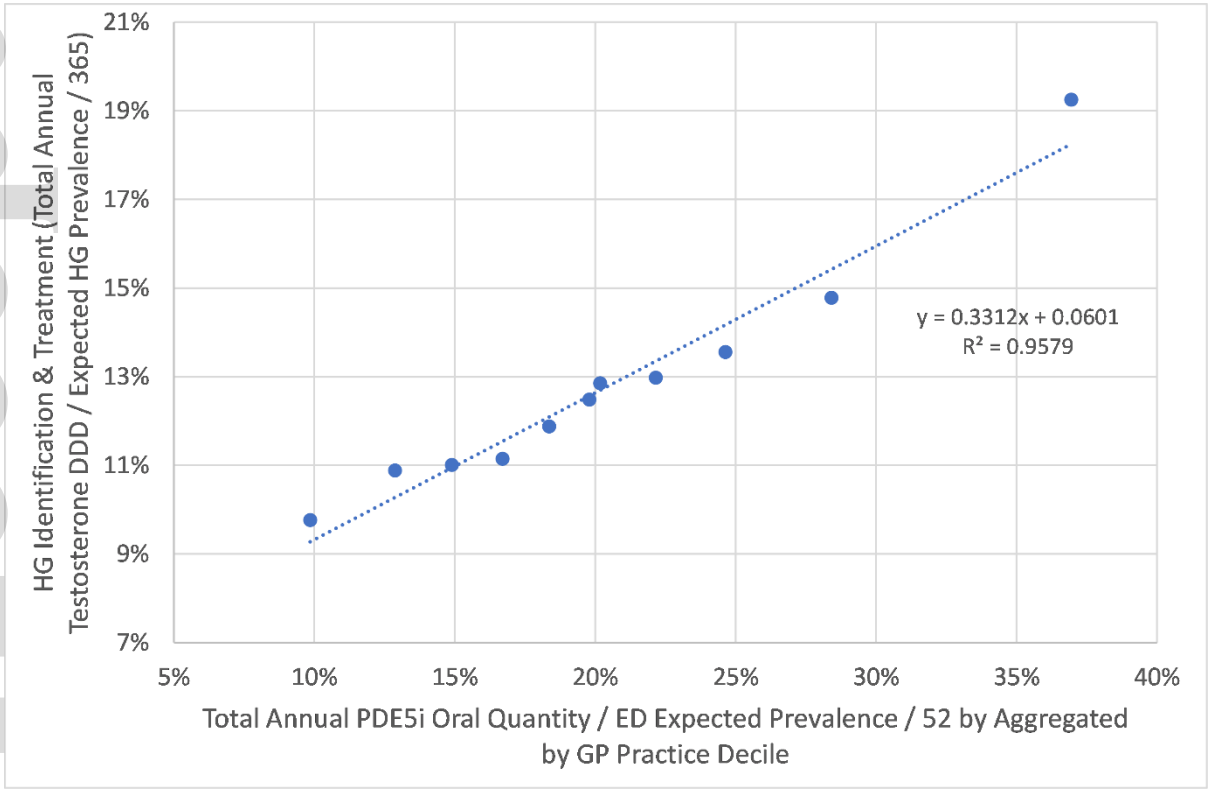

Figure 5